Remarks

In a telephone conversation with Examiner Carlson on October 27, 1993, Applicants provisionally elected, with traverse, to prosecute the invention of Group I, claims 1, 25-68, 99, and 100. Applicants hereby affirm this election. Of the elected claims, claims 25, 32, 34, 35, 38, 41-43, and 47-49 have been canceled. Claims 1, 26, 30, 36, 39, 40, 54, 55, and 62 have been amended. Claims 1, 26-31, 33, 36, 37, 39, 40, 44-46, 50-68, 99, and 100 remain in the application. No new matter has been added.

Rejection of claims 1, 25-68, 99, and 100 under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 1, 25-68, 99, and 100 under 35 U.S.C. §112, first paragraph, as the disclosure is enabling only for claims limited to the DNA encoding the CFTR protein of Figure 1 (Applicants assume that the Examiner is referring to Table I here rather than Figure 1). More particularly, the Examiner stated that

> [c]laims 1 and 36 are for any DNA encoding any CFTR and [c]laim 47 is for DNA encoding any CFTR activity. The specification only teaches how to make and use the CFTR disclosed and not other regulators of chloride current. It would require undue experimentation to determine proteins that are chloride regulatory channels other than CFTR, determine their activity, and acquire the DNA encoding the protein because it is not predictable what proteins are chloride channel regulators or if these proteins act in subunit form and are derived from different genes. Claim 50 is for any DNA comprising the synthetic "intron" in Fig. 6. The Claims should be limited to only that DNA encoding the CFTR or the synthetic intron on the instant invention and not other CFTR known or unknown. It would require undue experimentation to determine DNA having such an intron and if that intron would render the host expression of the DNA silent because it is not predictable if the intron depicted in Fig. 6 is an exon in other proteins, such as observed in splicing.

Applicants respectfully traverse this rejection. Claims 25, 32, 34, 35, 38, 41-43, and 47-49 have been canceled. Claims 1, 26 and 36 have been amended. Newly

amended claim 1 recites "a single DNA *comprising the nucleic acid sequence set forth in Table I which is further stabilized against cellular recombination.*" In similar manner claim 26, rewritten in independent form, references the sequence of Table 1 further "having at least one intron located within the cystic fibrosis transmembrane conductance regulator coding region." In like fashion, newly amended claim 36 recites "[a] low copy number vector comprising DNA *which encodes the amino acid sequence of cystic fibrosis transmembrane conductance regulator set forth in Table I.*" Claim 55 has been amended to delete reference to canceled claims 47 and 48. Claim 62 has been amended to depend from newly amended claims 1 and 36 rather than from canceled claims 25 and 28. These amendments are understood by Applicants to obviate the Examiner's rejection of claim 1 and the claims that depend therefrom (i.e., claims 28, 30-33, 63, and 64), claim 36 and the claims that depend therefrom (i.e., claims 37, 40, 46, 63, and 64), and claim 55 and the claims that depend therefrom (i.e., claims 56, 57, and 99). Cancellation of claims 25, 34, 35, 38, 41-43, and 47-49 and amendment of claims 1, 26, 36, 55, and 66 is done for the purpose of expediting prosecution of the present application and should not be construed as an acquiescence to the Examiner's §112 rejection.

Rejection of claims 35 and 40 under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 35 and 40 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner stated that "[i]n [c]laims 35 and 40 it is not clear what comprises a stabilizing agent or element for DNA and this term does not appear to be defined in the specification."

Applicants respectfully traverse this rejection. Applicants have canceled claim 35 and amended claim 40 to delete reference to "stabilizing element". Newly amended claim 40 recites "[t]he vector of claim 36 *wherein the DNA is stabilized against cellular*

recombination." The cancellation of claim 35 and the amendment of claim 40 are understood by Applicants to obviate the Examiner's rejection. Cancellation of claim 35 and amendment of claim 40 is done for the purpose of expediting prosecution of the present application and is not to be construed as an acquiescence to the Examiner's §112 rejection.

Rejection of claims 1, 28, 30-33, 35, 36, 37, 40, 46-49, 55-57, 63, 64, and 99 under 35 U.S.C. §102(e)

The Examiner rejected claims 1, 28, 30-33, 35, 36, 37, 40, 46-49, 55-57, 63, 64, and 99 under 35 U.S.C. §102(e) as being anticipated by Collins et al. (U.S. 5,240,846). According to the Examiner, Collins et al. teach vectors for the expression of the CFTR gene to be used in gene therapy. In addition, the Examiner asserted that

> Collins et al. deliver and express a single normal copy of the CFTR gene and this corrects the chloride regulatory defect in human colon tumor cell lines. Collins et al. teach silent mutations to stabilize the cloning of the gene (col. 3, 11). The transfer of the gene is by fusing the target cell to liposomes (col. 3, 15), plasmids, viral vectors, and retroviruses (col. 3). CFTR vectors are administered to the patient by injection, ingestion, or inhalation (col. 6).

Applicants respectfully traverse this rejection. Claims 32, 35, and 47-49 have been canceled. Claims 1, 36, 55, and 62 have been amended. Newly amended claim 1 recites "[a] single DNA *comprising a nucleic acid sequence set forth in Table 1 and which is further stabilized against cellular recombination.*" Newly amended claim 36 recites " [a] low copy number vector comprising DNA which encodes the amino acid sequence of the cystic fibrosis transmembrane conductance regulator as set forth in Table 1. Claim 55 has been amended to delete reference to canceled claims 47 and 48. As Collins et al. neither teach nor suggest the prevention of cellular recombination of the

DNA of Table 1 encoding CFTR nor the encoding of CFTR by the DNA of Table 1 having an intron, Collins et al. neither anticipates nor makes obvious newly amended claim 1 or the claims that depend therefrom (i.e., claims 28, 30-33, 35, 63, and 64), newly amended 26, newly amended claim 36 or the claims that depend therefrom (i.e., claims 30, 37, 40, 46, 63, and 64), newly amended claim 55 or the claims that depend therefrom (i.e., claims 56, 57, and 99) all of which now include reference to the sequence of Table 1. The Examiner is respectfully reminded that cancellation of claims 47-49 and amendment of claims 1, 26, 36, 55, and 62 is done for the purpose of expediting prosecution of the present application and should not be construed as an acquiescence to the Examiner's §102(e) rejection.

Rejection of claims 1, 26, 28, 32, 35, 47, 48, 55-57, 62-64 under 35 U.S.C. §102(a)

The Examiner rejected claims 1, 26, 28, 32, 35, 47, 48, 55-57, 62-64 under 35 U.S.C. §102(a) as being anticipated by Riordan, J.R. et al. (1989) *Science* 245:1066-1073. In support of this rejection, the Examiner asserted that

> Riordan et al. cloned the CFTR gene from epithelial cells (Claims 1, 28, 32, 47, 48, 55-57, 62-64). Most of the cDNA isolated contained sequence insertions corresponding to introns ((Claims 26, 35; page 1067, col. 1). The DNA was in single copy form (page 1069, col. 1). Fig. 6 teaches the DNA and amino acid sequences coding CFTR and position 508 is starred to show where the common deletion of Phe is located in mutated CFTR. Therein, these Claims are anticipated by Riordan et al.

Applicants respectfully traverse this rejection. Claims 32, 35, 47, and 48 have been cancelled. Claims 1, 26, 36, 55 and 62 have been amended as described above. As Riordan et al. neither teach nor suggest the expression of CFTR using the DNA of Table 1 encoding CFTR, Riordan et al. do not anticipate the claimed invention. Cancellation of claims 32, 35, 47, and 48 and amendment of claims 1, 26, 36, 55, and 62 is done without

prejudice and for the purpose of expediting prosecution of the present application and however, should not be construed as an acquiescence to the Examiner's §102(a) rejection.

Rejection of claims 29, 34, 41-45, 58, 60, 61, 65, 67, and 68 under 35 U.S.C. §103

The Examiner rejected claims 29, 34, 41-45, 58, 60, 61, 65, 67, and 68 under 35 U.S.C. §103 as being unpatentable over Collins et al., *supra*. According to the Examiner,

> [t]he teachings of Collins et al. are discussed above. Further, Collins et al. teach that the deletion of Phe at position 508 is the most common mutation in CFTR and CFTR defective cell lines can be used to diagnose CF and screen for carriers (col. 7). Though Collins et al. do not teach the vector of [c]laim 29, it would have been obvious to a person of ordinary skill in the art to make such a vector such that low copy numbers of CFTR are expressed because Collins et al. teach low copy vectors to prevent cell death during the expression of CFTR (col. 2). Collins et al. teach that the DNA encoding CFTR (col. 16+) and this sequence is nearly identical (99%) to that of the instant application but for a single base change at nucleotide 1990. This single base change may be incidental. None-the-less, this changes the Applicants' His to Asn at position 620, over 100 amino acids away from the known active region of CFTR at position 508. Therein, it would have been obvious to a person of ordinary skill in the art that these sequences encode the same protein ([c]laim 34). Collins et al. teach that the most common mutation occurs at amino acid position 508 with the deletion of Phe. Therein, it would have been obvious to a person of ordinary skill in the art to delete the DNA codon encoding amino acid position 508 in low copy vectors to express the mutated CFTR because Collins et al. teach the use of such systems for diagnosing CF ([c]laims 41-45). Collins et al. express the CFTR in mammalian cell lines rendering it obvious to a person of ordinary skill in the art to express CFTR in other mammalian cell lines such as CHO and C127 ([c]laims 58, 65). Collins et al. cloned the CFTR. Collins et al. do not teach that they cloned in E. coli though they did use appropriate vectors and promoters for cloning in E. coli. Therein, it would have been obvious to a person of ordinary skill in the art to express the CFTR gene in low copy vectors in E. coli because Collins et al. most likely cloned expressed CFTR in low copy vectors in E. coli based on the promoters and vectors that they used ([c]laims 60, 61, 67, and 68).

Applicants respectfully traverse this rejection. Claims 34 and 41-43 have been canceled. Claims 1, 26, 36, 55, and 62 have been amended as described above. Collins et al. neither teach nor suggest the expression of CFTR using the DNA sequence of Table 1. As claim 29 depends from newly amended claim 1, claims 44 and 45 depend from newly amended claim 36, claims 58, 60, and 61 depend from newly amended claim 55, and claims 65, 67, and 69 depend from newly amended claim 62, all of these claims, as well as claim 26, which reference Table 1, are unonobvious in view of Collins et al. Applicants note that cancellation of claims 34 and 41-43 and amendment of claims 1, 26, 36, 55, and 62 is done for the purpose of expediting prosecution of the present application is not an acquiescence to the Examiner's §103 rejection, and is without prejudice to their later presentation.

Rejection of claims 34, 49, 58, 60, 61, 65, 67, and 68 under 35 U.S.C. §103

The Examiner rejected claims 34, 49, 58, 60, 61, 65, 67, and 68 under 35 U.S.C. §103 as being unpatentable over Riordan et al., *supra*. According to the Examiner,

> Riordan et al. discloses the cDNA for the CFTR gene. This cDNA is 99% identical to that disclosed by the Applicants, with only a single base change [at] position 1990. The Applicants state on page 13 that their cDNA sequence is markedly different from the cDNA disclosed by Riordan et al. This is not the case because the Applicants admit that they have acquired the Riordan et al. clones form ATCC (page 10) and, in their 1990 paper published in Nature they state that the "DNA sequence analysis of the complete sequence revealed a sequence identical to that reported by Riordan et al., with the exception that the base at position 1990 is C rather than A". This single base change may be incidental. None-the-less, this changes the Applicants His to Asn at position 620, over 100 amino acids away from the known active region of CFTR at position 508. Therefore, the cDNA sequence encoding the CFTR gene is obvious over Riordan et al. because with only a single base difference between these two long sequences it would have been obvious to persons of ordinary skill in the art that the two sequences code for the same protein, that is, CFTR. Riordan et al. expressed the CFTR from epithelial cells; therein, it would have been obvious to a person of ordinary skill in the art

that CFTR could be expressed from other mammalian cell lines such as CHO and C127.

Applicants respectfully traverse this rejection. Claims 34 and 49 have been canceled. Claims 1, 26, 36, 55 and 62 have been amended as previously described above. Claims 58, 60, and 61 depend from newly amended claim 55. Claims 65, 67, and 68 depend from newly amended claim 62. As Riordan et al. neither teach nor suggest the expression of CFTR using the DNA of Table 1 recited in claim 1 from which both claims 55 and 62 depend and accordingly, cells containing such stabilized DNA are also imbued with nonobviousness over teachings of Riordan et al. Cancellation of claims 34 and 49 and amendment of claims 1, 26, 36, 55, and 62 has been done for the purpose of expediting prosecution of the present application, is without prejudice and should not be construed as an acquiescence to the Examiner's §103 rejection.

Rejection of claims 30, 31, 99, and 100 under 35 U.S.C. §103

The Examiner rejected claims 30, 31, 99, and 100 under 35 U.S.C. §103 as being unpatentable over Riordan et al., *supra*, as applied to claims 34, 49, 60, 61, 65, 67, and 68 above, and further in view of Sambrook et al. (1989). More particularly, the Examiner stated that

> Riordan et al. cloned the DNA from the region of the CF locus (page 1066, col. 2) to isolate the cDNA encoding the CFTR gene. Riordan et al. do not teach which phages or cosmids that they used to clone the cDNA, probably because cloning is a technique that is well-known and widely used in the art. However, Sambrook et al. teaches that bacteriophage lambda and cosmid vectors are routinely used for cloning DNA (page 9.4). Sambrook et al. also teaches that cosmids serve as vehicles to introduce the recombinant genomes into bacteria where [they] are propagated as large plasmids (Claim 2). In Chapter 16, Sambrook et al. teach the expression of proteins from cloned genes (pages 16.2+ and 16.30+; Claims 4, 5, 6, and 14). Taken together, it would have been obvious to one of ordinary skill in the art at the time the invention was made to insert the DNA into the phages/plasmids and insert the compositions into cells

because the cDNA was cloned in a phage or plasmid by Riordan et al. and Sambrook et al. teaches that cDNA can be used to transfect cells.

Applicants respectfully traverse this rejection. Claims 1, 26, 36, 55, and 62 have been amended as described above. Claims 30 and 31 depend from newly amended claim 1, and claim 30 also depends from newly amended claim 26. Claim 99 depends from newly amended claim 55. Claim 100 depends from newly amended claim 62. As Riordan et al. neither teach nor suggest the prevention of the inappropriate expression of CFTR using the DNA of Table 1 either stabilized against cellular recombination (claim 1) or further comprising an intron in the CFTR coding region (claim 26), phages or plasmids containing such DNA (claims 30 and 31) and methods using host cells transformed with such DNA for production of CFTR (claims 99 and 100) are nonobvious in view of the teachings of Riordan et al. whether alone or in combination with the teachings of Sambrook et al. Amendment of claims 1, 26, 36, 55, and 62 is done without prejudice for the purpose of expediting prosecution of the present application and should not be construed as an acquiescence to the Examiner's §103 rejection.

Rejection of claim 33 under 35 U.S.C. §103

The Examiner rejected claim 33 under 35 U.S.C. §103 as being unpatentable over Riordan et al., *supra*, and Sambrook et al. and further in view of Nichols (1988). The Examiner asserted that

> [w]ith the disclosed cDNA sequence by Riordan et al. and the teachings of Sambrook et al. on how to transform eukaryotic cells to express proteins encoded by cDNA, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a therapeutic composition with the cDNA encoding CFTR. This concept is supported by Nichols who teaches that somatic gene therapy in which a product expressed by a normal gene would function in place of the defective gene product would be a viable method of treating cystic fibrosis.

Applicants respectfully traverse this rejection. Claim 33 ultimately depends from newly amended claim 1 which recites "[a] single DNA *comprising the nucleic acid sequence set forth in Table 1 which is further stabilized against cellular recombination.*" As Riordan et al. neither teach nor suggest the expression of CFTR using the sequence set forth in Table 1, the teachings of the cited references utterly fail to render obvious the claimed invention particularly as now set forth in the newly amended claims. Amendment of claim 1 is done without prejudice for the purpose of expediting prosecution of the present application and is not to be construed as an acquiescence to the Examiner's §103 rejection.

Conclusion

In view of the amendments and remarks set forth above, it is respectfully submitted that this application is in condition for allowance. Applicants would be grateful for favorable consideration thereof. If the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,

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